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Epidemiology of Minimal Breast Cancer

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• **A case-control study conducted within the Breast Cancer Detection Demonstration Project allowed comparison of epidemiologic factors for benign breast diseases (n=1,404), in situ cancer (n=199), small (≤1 cm) invasive cancer (n=210), and larger invasive cancer (n=788). Control subjects consisted of program participants who were not recommended for breast biopsy. Relationships were similar for small and larger invasive tumors, both showing associations with family history of breast cancer, age at first live birth, history of bilateral oophorectomy, and obesity. In situ cancer was affected by family history and age at first childbirth but not by oophorectomy or obesity. These findings support the notion that "minimal" breast cancer is indeed cancer. In addition, the results suggest that hormonal influences early in life may initiate the carcinogenic process, while those that operate later may enhance the progression from in situ to invasive disease.**

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WIDESPREAD programs for the early detection of breast cancer have enabled the recognition of increasing numbers of in situ and relatively small invasive cancers. This has led to concern over whether these minimal cancers are biologically related to the larger tumors often detected by the patient herself[1] and to debate over appropriate management and therapy, particularly for the in situ tumors.[2] In an effort to clarify the epidemiologic patterns of minimal breast cancer, we compared risk factors for benign conditions, in situ carcinomas, small invasive lesions, and larger invasive carcinomas diagnosed within the context of a large multicenter breast cancer screening program.

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SUBJECTS AND METHODS

Study subjects were selected from the Breast Cancer Detection Demonstration Project (BCDDP), a screening program involving more than 280,000 women at 29 widely dispersed centers. This program, begun in 1973 and jointly sponsored by the American Cancer Society and the National Cancer Institute, recruited women for a five-year program of annual breast examinations by combined modalities of physical examination, mammography, and thermography. The present investigation included all cases of breast cancer diagnosed in the study population from July 1973 through May 1977. For 66 of these cases, there was some disagreement regarding the diagnosis,[3] and these women were not approached for interview. A sample of participants whose biopsy specimens showed benign breast disease was also chosen, as was a comparison group of women who had neither undergone a biopsy nor received a recommendation for a surgical evaluation while in the program. These benign and control subjects were chosen to approximate the patients with breast cancer on the following factors: center, race (white, black, Oriental, other), age (same five-year group), time of entry (same six-month period), and length of continuation in the program.

Home interviews were conducted by standardly trained nurse interviewers. Completed interviews were obtained from 1,552 subjects with breast cancer (86.1% of eligible subjects), 1,566 benign subjects (85.2%), and 1,375 controls (74.2%). The subjects with breast cancer were interviewed at various intervals after diagnosis. In the analyses, however, exposure information was truncated at the time of diagnosis for cases and at the equivalent time for controls. A number of women (60 with breast cancer, 23 with benign conditions, and nine controls) reported a history of breast cancer before entering the program and were excluded from the present analysis. We also restricted analysis to white subjects (who composed 91% of the entire population). The final study group consisted of 1,362 breast cancer cases, 1,404 benign cases, and 1,250 controls.

Based on a standardized reporting system, all breast cancer cases were classified as in situ or invasive. Standardized pathological information was unavailable for 165 cases, and these were analyzed separately. For the invasive cases, information on tumor length, width, and depth was reviewed for those mastectomy specimens that allowed adequate evaluation. Invasive lesions in which each dimension was less than or equal to 1 cm were classified as small invasive cancer, and all others as larger invasive cancer. Those specimens with inadequate information on size were classified as larger invasive lesions. A total of 788 breast cancer cases were classified as larger invasive cancers, 210 as small invasive cancer, and 199 as in situ cancer. When analyses were conducted defining small invasive cancer as less than 1 cm (133 cases), the results were nearly identical to those reported herein for small invasive disease.

Table 1.—Relative Risks* (95% Confidence Intervals) of Breast Diseases, by Family History of Breast Cancer

	Disease Classification			
			Invasive	
	Benign (n=1,404)	In Situ (n=199)	≤1 cm (n=210)	>1 cm (n=788)
First-degree relative	1.19 (0.9-1.5)	1.67 (1.1-2.5)	2.51 (1.7-3.6)	2.00 (1.6-2.6)
Mother	1.30 (0.9-1.8)	1.86 (1.1-3.1)	2.13 (1.3-3.5)	1.94 (1.4-2.7)
Sister	1.07 (0.8-1.5)	1.36† (0.7-2.6)	2.70 (1.7-4.4)	2.31 (1.7-3.2)

*Adjusted for age at diagnosis.
†Based on fewer than 20 cases.

Table 2.—Relative Risks of Breast Diseases, by Reproductive History, Menstrual Factors, and Previous Breast Diseases

	Disease Classification			
			Invasive	
	Benign (n=1,404)	In Situ (n=199)	≤1 cm (n=210)	>1 cm (n=788)
Ever pregnant*				
No	1.00	1.00	1.00	1.00
Yes	0.97	1.00	0.74	0.98
95% confidence interval	0.8-1.2	0.6-1.6	0.5-1.1	0.7-1.3
Age at first live birth,* yr				
<20	1.00	1.00	1.00†	1.00
20-24	1.04	1.97	1.30	1.25
25-29	0.96	2.36	1.61	1.64
≥30	1.26	2.68	2.17	2.29
Nulliparous	1.11	2.35	1.74	1.80
χ_1 for trend‡	1.01	3.06§	2.73§	4.69‖
Age at menarche,* yr				
<12	1.00	1.00	1.00	1.00
12	1.01	0.97	1.04	0.80
13	0.92	0.84	0.87	0.84
14	1.10	1.19	1.01	0.87
≥15	0.80	1.07	1.05	0.66
χ_1 for trend	−1.32	0.25	0.18	−2.71§
Type of menopause¶				
Natural menopause	1.00	1.00	1.00	1.00
Hysterectomy only	0.92	1.25	1.02	0.97
Ovaries removed	0.87	0.93	0.83	0.73
Previous breast biopsy*				
No	1.00	1.00	1.00	1.00
Yes	1.68	2.08	1.09	1.23
95% confidence interval	1.4-2.0	1.5-2.9	0.7-1.6	0.9-1.6
No. of biopsies*				
1	1.43	1.61	0.92	1.15
≥2	2.32	3.24	1.55†	1.44
χ_1 for trend	6.01‖	5.06‖	0.99	2.12#

*Relative risks adjusted for age at diagnosis.
†Based on fewer than 20 cases.
‡Nulliparous women excluded from trend.
§$P<.01$.
‖$P<.001$.
¶Relative risks adjusted for age at diagnosis and menopausal hormone use.
#$P<.05$.

Maximum likelihood techniques were utilized for deriving combined estimates of relative risk (RR) and corresponding 95% confidence intervals.[4] When the 95% confidence interval did not include unity, the RR was considered statistically significant ($P<.05$). For multiple levels of exposure, statistical significance was assessed using a one-tailed linear trend test.[5]

RESULTS

A comparison of age distributions showed little difference between women with small and larger invasive disease, with the proportions younger than 45 years of age being 10.0% and 11.9%, respectively. A larger proportion (17.1%) of the women with in situ cancer were younger (<45 years of age) at diagnosis. Because of these age discrepancies, all results were inspected for consistency by age, and age-adjusted RRs derived.

A history of breast cancer in a first-degree relative was associated with a similar and statistically significant risk for all pathological stages of malignancy, being 1.7, 2.5, and 2.0 for in situ, small invasive, and larger invasive disease, respectively (Table 1). When investigated by type of relationship, significant RRs of approximately twofold were associated with a family history of breast cancer in a mother for all three categories of malignancy. Excess risks of approximately 2.5-fold were associated with a family history of breast cancer in a sister for the two forms of invasive cancer and a nonsignificant RR of 1.4 for in situ disease. In contrast, no significant risk of benign disease was associated with a family history of breast cancer (RR=1.2 for family history in a first-degree relative).

A history of ever being pregnant was not associated with a significant reduction in risk for any form of breast cancer (Table 2). Significant ($P<.01$) trends, however, were seen in all malignant categories according to age at which the first child was born, with women having their first child after age 30 years showing RRs on the order of 2.2 to 2.7 compared with those having a child before 20 years of age. No trend in risk of benign disease was observed according to age at first birth.

A significant decreasing trend in risk of larger invasive lesions was seen with increasing ages at menarche. Women who began menstruating at 15 years of age or later had a 34% lower risk than those whose menarche was before 12 years of age. No relationship with age at menarche was seen for small invasive cancer, in situ lesions, or benign conditions. Among menopausal women, 27% and 17% reductions in risk of larger and small invasive cancers, respectively, were seen for women having undergone a bilateral oophorectomy compared with those having had a natural menopause. No substantial

Table 3.—Relative Risks* of Breast Diseases, by Weight, Height, and Quetelet's Index

	Disease Classification			
			Invasive	
	Benign (n=1,404)	In Situ (n=199)	≤1 cm (n=210)	>1 cm (n=788)
Weight, kg				
<56.6	1.00	1.00	1.00	1.00
56.6-63.3	1.14	0.70	1.04	1.11
63.4-70.0	1.18	0.82	1.07	1.34
≥70.1	1.12	1.03	1.07	1.44
χ_1 for trend	1.00	0.33	0.35	3.14†
Height, cm				
<157.5	1.00	1.00	1.00	1.00
157.5-162.5	0.77	1.15	1.33	1.07
162.6-167.5	0.80	0.91	1.41	1.19
≥167.6	0.77	1.41	1.55	1.28
χ_1 for trend	−1.55	1.10	1.50	1.78‡
Quetelet's index§				
<22	1.00	1.00	1.00	1.00
22-23	0.93	0.99	0.80	1.06
24-25	1.14	1.10	0.73	1.11
≥26	1.12	0.81	0.84	1.27
χ_1 for trend	1.65‡	−0.82	−0.90	2.06‡

*Adjusted for age at diagnosis.
†$P<.01$.
‡$P<.05$.
§Quetelet's index: (weight [in kilograms] divided by height [in centimeters] squared)×100.

Table 4.—Relative Risks* of Breast Diseases, by Education, Income, and Marital Status

	Disease Classification			
			Invasive	
	Benign (n=1,404)	In Situ (n=199)	≤1 cm (n=210)	>1 cm (n=788)
Education, yr				
<12	1.00	1.00	1.00	1.00
12	0.82	1.37	1.07	0.90
13-16	0.88	1.53	1.38	1.10
≥17	0.78	1.55†	1.60	1.10
χ_1 for trend	−0.71	1.51	2.16‡	1.60
Family income				
<$10,000	1.00	1.00	1.00	1.00
$10,000-$19,000	1.31	1.69	1.14	1.12
$20,000-$29,000	1.04	1.60	1.26	0.90
≥$30,000	1.02	1.50	1.10	1.06
Unknown	1.01	1.44	0.78	0.96
χ_1 for trend§	0.32	1.36	0.29	1.01
Marital status				
Married	1.00	1.00	1.00	1.00
Single	0.99	1.01†	0.86†	1.17
Divorced/separated	0.92	0.98†	1.36†	1.00
Widowed	0.98	1.42	1.19	1.06

*Adjusted for age at diagnosis.
†Based on fewer than 20 cases.
‡$P<.05$.
§Unknowns excluded from trend.

reductions in risk of in situ disease or benign conditions were associated with bilateral oophorectomy.

A history of a benign breast biopsy was associated with a significant increase in risk for both in situ cancer (RR=2.1) and benign disease (RR=1.7) (Table 2). Previous biopsy was associated with only 10% to 20% elevations in risk of small and larger invasive cancers, neither RR being significant. Multiple biopsies (two or more) were related to 50% excess risks, however, for both small and larger invasive malignant neoplasms, and risks of 3.2 and 2.3 were seen for in situ cancer and benign disease, respectively.

Table 3 presents risk estimates according to weight, height, and Quetelet's index, a measure of obesity. A significant linear trend in the risk of larger invasive disease was noted according to weight. Those women in the highest weight category (≥70 kg) were at approximately a 50% elevated risk compared with those in the lowest category. No trends in risk were observed according to weight for the other categories of breast disease. The lack of a weight or oophorectomy effect for in situ disease was not due to those women being somewhat younger than those with invasive disease, as no associations were noted for either those younger than 55 years or those older than this. The risk of larger invasive cancers also rose with increasing height and Quetelet's index, although the relationships were weaker than those noted for weight. No significant trends were seen according to these measures for the other types of breast disease.

Risk of in situ and small invasive cancer increased with increasing years of education, reaching a RR of 1.6 for those with postcollege education as compared with those with less than a high school education (Table 4). This trend of risk was statistically significant ($P<.05$) for small invasive disease but of borderline significance ($P=.07$) for in situ cancer. Although a trend ($P=.06$) was seen according to years of education for larger invasive cancer, this was due primarily to differences between those with less than a high school education and those with more advanced education, since there was little evidence of a trend over all of the educational categories. No relation was observed between years of education and risk of benign disease. Family income and marital status showed no clear association with risk of any of the breast conditions.

Risk factors were also assessed for the 165 cases that had not been classified as in situ or invasive at the time of analysis. These cases showed relationships similar to those observed for larger invasive disease, including significant associations with a family history of breast cancer in a first-degree relative (RR=2.5), significant linear trends according to age at first live birth (χ for trend=5.2) and age at menarche ($\chi=-2.5$), and a slightly elevated risk

for those with multiple breast biopsies (RR=1.4).

COMMENT

This analysis showed close similarity between the risk factors for small and larger invasive tumors, supporting the notion that these conditions are biologically closely related. In addition, the identified risk factors and their magnitude generally corresponded to the well-established epidemiology of breast cancer diagnosed outside of a screening context. Both the small and larger invasive tumors displayed approximately twofold excess risks associated with a family history of breast cancer in any first-degree relative, with slightly higher risks when the affected relative was a sister. These findings are similar to those found for breast cancer by a number of other investigators.[6,7] In addition, for both small and larger invasive tumors, risk increased in a manner traditionally associated with the age at which a woman has her first child.[8] The RRs were on the order of 2.2 for women who delayed their first birth until 30 years of age or later, as compared with those with a child before 20 years of age. Consistent with other observations,[9,10] lower risks were seen for both categories of invasive disease among women who underwent bilateral oophorectomy. Some variation between small and larger invasive cancer, however, was noted for age at menarche and weight relationships. Age at menarche was significantly inversely related to risk of larger invasive tumors, but no relationship was observed with the small invasive lesions. This trend, however, when observed in other studies,[11] has been slight, and the number of small invasive cases may have been insufficient to detect an association. In addition, weight was slightly related to risk of small invasive lesions, showing a pattern intermediate to that observed for in situ cancer and larger invasive cancer. This latter finding is consistent with the relationship to obesity observed elsewhere, primarily among postmenopausal women.[12-14]

Two risk factors traditionally noted for breast cancer, nulliparity and a history of surgically confirmed benign breast disease, were not predictive of risk for either the small or larger invasive lesions. Risk was not significantly elevated for nulliparous compared with parous women. This did not stem from lower than usual risks among nulliparous women in the screening program, but rather from higher risks among parous women, resulting from their having an older average age at first birth compared with other populations studied. This was evident from the fact that the risk of nulliparous women corresponded to that of women who had their first child in their late 20s. Women with a history of breast biopsy also showed no significant elevation in RR. This was similar to a previous observation among BCDDP participants[15] and probably reflects self-selection of women who have a history of biopsy for "low-risk" lesions into this screening program. A history of multiple prior biopsies, however, was associated with 50% excess risks of both categories of invasive disease.

Risk factors for in situ cancer resembled the customary predictors of risk noted for invasive tumors. The correspondence, however, was not as close as that noted between the small and larger invasive lesions. Significant associations of an expected magnitude were associated with a family history of breast cancer, particularly in the mother, as well as with age at first birth and level of education. Nulliparity acted as a risk factor in a manner similar to that observed for invasive malignant neoplasms, with the RR for in situ disease among nulliparous women corresponding to that for women who had a first child in their late 20s. Unlike the observations for invasive disease, however, no associations were noted with either weight or oophorectomy. It is possible that these differences were due to chance because of the relatively small number of in situ compared with invasive cases. It did not appear, however, as though the differences resulted from variations in age distributions, as examination of age-specific risks did not alter interpretations. Although based on small numbers, there was no increased risk of in situ cancer with a history of breast cancer in a sister. In addition, lower RRs were not seen for those with older ages at menarche, a finding consistent with that observed for the small invasive lesions and one that may reflect the limited number of cases involved. Finally, a sharp increase in the RR of in situ disease was associated with a history of multiple benign breast biopsies; this resembled the pattern for benign disease more closely than that for either of the categories of invasive cancer.

It is noteworthy that except for a prior breast biopsy, a well-established risk factor for benign disease,[16] no associations were noted between the development of benign breast disease and any breast cancer risk factors investigated among the very large series of patients whose biopsy specimens were nonmalignant during this screening program. This probably reflects the broad nature of the classification of benign breast disease. Further analyses utilizing more refined pathological definitions of benign disease should help identify and characterize those lesions that are more closely related to breast cancer.

Because of the virtually identical profile of risk factors, the small invasive lesions would appear to share the same pathological mechanisms with the larger tumors. Furthermore, the risk factors detected for in situ cancer support the contention that this disease is biologically closer to invasive breast cancer than to benign breast disease. The few discrepancies, however, in risk factors between in situ and invasive disease suggest that the two conditions are at different stages in the process of malignant transformation and are not biologically identical. Both in situ and invasive cancers share several risk factors that operate early in reproductive life (history of breast cancer in the mother, parity, and age at first birth), whereas in situ disease is not affected by risk factors that operate later in life (oophorectomy, obesity). This may indicate that early risk factors are associated with the initiation and promotion of the carcinogenic process, while the hormonal influences of oophorectomy and obesity operate to inhibit or enhance the progression to invasive disease. For now, this must remain speculative, since other explanations are possible. For example, the increased risk for larger invasive lesions among obese women may

reflect an inability in heavier women to detect breast cancer at early stages. By continued study of this screening population and enhancement of numbers of incident cancers, it should be possible to distinguish between alternative explanations and to clarify the risk profile of women who would benefit most from screening programs.

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